The depth and complexity of this intermixture is revealed in a 1740 slave code in South Carolina: all Negroes and Indians, *(free Indians in amity with this government, and Negroes, mulattos, and mustezoes, who are now free, excepted)* mulattos or mustezoes who are now, or shall hereafter be in this province, and all their issue and offspring...shall be and they are hereby declared to be, and remain hereafter absolute slaves.

Millions of Native Americans were also enslaved, particularly in South America

In the American colonies in 1730, nearly 25 percent of the slaves in the Carolinas were Cherokee, Creek, or other Native Americans

The situation of enslaved Indians varied among the tribes. In many cases, enslaved captives were adopted into the tribes to replace warriors killed during a raid. Enslaved warriors sometimes endured mutilation or torture that could end in death as part of a grief ritual for relatives slain in battle. Some Indians cut off one foot of their captives to keep them from running away; others allowed enslaved captives to marry the widows of slain husbands.

Once Europeans arrived as colonialists in North America, the nature of Indian slavery changed abruptly and dramatically. Indians found that British settlers, especially those in the southern colonies, eagerly purchased or captured Indians to use as forced labor in cultivating tobacco, rice, and indigo. More and more, Indians began selling war captives to whites rather than integrating them into their own societies. And as the demand for labor in the West Indies became insatiable, whites began to actively enslave Indians for export to the so-called "sugar islands."

The resulting Indian slave trade devastated the southeastern Indian populations and transformed Native American tribal relations throughout the region. The English at Charles Town, the Spanish in Florida, and the French in Louisiana sought trading partners and allies among the Indians, offering trading goods such as metal knives and axes, firearms and ammunition, intoxicants and beads, and cloth and hats in exchange for furs (deerskins) and Indian slaves captured from other tribes. Unscrupulous traders, frontier settlers, and government officials encouraged Indians to make war on other tribes to reap the profits from the slaves captured in such raids or to weaken the warring tribes.

It is not known how many Indians were enslaved by the Europeans, but they certainly numbered in the tens of thousands. It is estimated that Carolina merchants operating out of Charles Town shipped an estimated 30,000 to 50,000 Indian captives between 1670 and 1715 in a profitable slave trade with the Caribbean, Spanish Hispaniola, and northern colonies. Because of the higher transportation costs of bringing blacks from Africa, whites in the northern colonies sometimes preferred Indian slaves, especially Indian women and children, to blacks. Carolina actually exported as many or even more Indian slaves than it imported enslaved Africans prior to 1720. The usual exchange rate of captive Indians for enslaved Africans was two or three Indians to one African.

Until late in the 18th century, Indian slaves worked on English plantations along side African slaves and even, occasionally, white indentured servants.

A similar pattern of friendly and then hostile relations among the English and Indians followed in the southeastern colonies. For example the Creek, a loose confederacy of many different groups who had banded together to defend themselves against slave-raiding, allied with the English and moved on the Apalachee in Spanish Florida, destroying them as a group of people in the quest for Indian slaves. These raids also destroyed several other Florida Indian tribes, including the Timucua. Indeed, most of the colonial-era Indians of Florida were killed, enslaved, or scattered. It is estimated that English-Creek raids on Florida yielded 4,000 Indian slaves between 1700 and 1705.

The Indian wars of the early 18th century combined with the growing availability of African slaves essentially ended the Indian slave trade by 1750.